REMARKS

Claims 3, 4, 6-8, 35-41, 60, 61, 66-69, and 102-116 are pending. Claims 6, 61, 66, and 67 are amended herein. Claims 117-121 are added. Support for the amendments to claims and added claims is found throughout the Specification and claims, as filed, and no new matter is presented by the amendment.

Favorable reconsideration in light of the amendments are remarks which follow a respectfully requested.

1. 35 U.S.C. §112 Rejections

Claims 6, 61, 66, 67, and 102 are rejected under 35 U.S.C. §112, second paragraph.

Applicants have amended the claims as suggested. In particular, applicants amended claims 6, 61, 66, 67, and 102 to delete wording such as e.g., preferably, typically, specially, etc., and have added claims 117-121 to set forth the deleted items from claims 6, 61, 66, 67, and 102.

Reconsideration and withdrawal of the rejection is respectfully requested.

2. 35 U.S.C. §112 Rejections

Claims 3, 6, 7, 35, 60, 61, 66-69, 102, 103, and 111-116 are rejected under 35 U.S.C. §102(b) over WO 98/17255 (hereinafter '255). Applicants respectfully traverse.

Applicants teach a method for controlling the flux of penetrants across an adaptable semi-permeable porous barrier. Prior to Applicants' teaching, it was believed that the channels in the skin through which highly deformable droplets migrate spontaneously across the stratum corneum, while unknown, possess properties that are sufficiently constant to reveal little inter-site, inter-individual, inter-species or inter-carrier variability. It was found that the relative bio-availability of different drugs in the blood after an epicutaneous administration in highly adaptable droplets (Transfersomes) is fairly constant. It was believed that pore

distribution depends little on the nature of the penetrant or the drug. It was further believed that the dose affects merely the depth of penetrant and drug distribution.

Applicants surprisingly found, contrary to the previous conclusions and beliefs, that by changing the applied dose above a certain threshold and in a sufficiently wide range not only affects the drug/penetrant distribution, but also determines the rate of penetrant transport across the barrier. As such, Applicants discovered that is is possible to control the rate of transcutaneous drug delivery when highly deformable carriers are used. This provides significant imprivements in the delivery of drugs through the skin.

In the present claims, Applicants claim methods, kits, and devices for controlling flux of transfersomes across the skin. Applicants methods, kits, and devices make it possible to specifically and predictably control the rate of transcutaneous drug delivery when transfersomes are used.

The '255 reference does not teach or suggest a method for controlling the delivery of drugs through the skin or the flux of transfersomes through the skin. As set forth, prior to Applicants' teaching, it was not even recognized that it could be possile to specifically and predictably control to rate of transcutaneous drug delivery when transfersomes are used or how this could be accomplished. The '255 reference is completely silent as to how the flux of penetrants ("fluid droplets") can be controlled across a barrier (e.g. skin). The '255 referencs doesn't even teach or suggest that such control is possile. Further, the '255 reference does not teach or suggest that the selection of the dose amount of drug has anything to do with the flux of the vesicles through the skin.

In sum, Applicants teach methods, kits, and devices for producing predictable flux across the skin. Applicants unexpectedly found that the use of different amounts of identical formulations will produce a specific and predictable controled rate of transcutaneous drug delivery when transfersomes are used. This finding is counter-intuitive and has not been taught or suggested by the prior art. On the contrary, a

skilled person would have through that the flux across a semi-permeale barrier follws the first law of diffusion (Fick's law) and is governed by the characteristics of the formulation (penetrant characteristics) rather than by volume (penetrant amount). In contrast, Applicants teach that penetrant concentration in a corresponding formulation does not govern but, rather, the applied amount of penetants is the most important factor of barrier transport.

As provided in MPEP-2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Or stated another way, "The identical invention must be shown in as complete detail as is contained in the ... claims. *Richardson v Suziki Motor Co.*, 868 F.2d 1226, 9 USPQ 2d. 1913, 1920 (Fed. Cir. 1989). Although identify of terminology is not required, the elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

It is clear from the foregoing remarks that the above-identified claims are not anticipated by the '255 reference. The '255 reference fails to teach or suggest a method for controlling the flux of penetrants across an adaptable semi-permeable porous barrier. Among other things, the '255 reference fails to teach or suggest that the flux of penetrants across the barrier is or could possibly be controlled by selecting a dose amount of penetrants to be applied on a predetermined area of the barrier. The '255 reference further fails to teach kits or patches whereby the kits and patches control the flux of penetrants as set forth.

Accordingly, claims 3, 35, and 60 are patentable over the '255 reference. Claims 4, 6-8, 36-41, 61, 66-69 and 102-120 depend from claims 3, 35, and 60 and, likewise, are patentable over the '255 reference. Reconsideration and withdrawal of the rejection is respectfully requested.

3. 35 U.S.C. §103 Rejections

Claims 3,4, 6-8, 35, 41, 60-61, 66-69, and 102-116 are rejected under 35

U.S.C. §103(a) over WO 98/17255 (hereinafter '255) in view of Unger (6,028,066)(hereinafter '066). Applicants respectfully traverse.

As set forth above, the '255 reference does not teach or suggest a method, kit, or patch for controlling the flux of penetrants across an adaptable semi-permeable porous barrier, wherein the dose amount of penetrants to be applied on a predetermined area of the barrier is selected to control the flux across the barrier. The '066 reference fails to remedy these deficiencies in the '255 reference.

The '066 reference describes prodrugs comprising fluorinated amphiphiles and does not relate to transfersomes, much less transfersome mediated flux across barriers. While the '066 reference mentions vehicles, liposomes, bubbles, and a multitude of other vesicle types (col. 4, lines 9-58), there is no teaching of transfersomes.

Applicants note that transfersome mediated drug delivery through barriers is very different than customary drug delivery through barriers. In particular, other types of aggregates (liposomes, niosomes, nanoparticles, microemulsions, etc.) act as simple drug reservoirs on the skin: the aggregates, having insufficient deformability and/or stability, are incapable of crossing the barrier. Rather, they remain on the skin while the drug is released gradually from the vehicle to then diffuse through the skin barrier on its own. Transfersomes, on the other hand, are highly deformable droplets that deform and penetrate the barrier (e.g. skin), thereby delivering the drug through the skin.

Thus, the '066 reference does not teach or suggest transfersomes. Further, the '066 reference does not teach or suggest a method, kit, or patch for controlling the flux of penetrants across an adaptable semi-permeable porous barrier, wherein the dose amount of penetrants to be applied on a predetermined area of the barrier is selected to control the flux across the barrier. As set forth above, '066 does not teach or suggest transfersomes, much less the control of the flux of transfersomes across barriers.

Accordingly, claims 3, 35, and 60 are patentable over the '255 and '066 references. Claims 4, 6-8, 36-41, 61, 66-69 and 102-120 depend from claims 3, 35, and 60 and, likewise, are patentable over the '255 and '066 references. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant respectfully requests early consideration and allowance of the subject application.

Applicants believe that additional fees are not required in connection with the consideration of the within matter. However, if for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105.**

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,

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